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(54) **Title:** PROCESS FOR A HOMOGENEOUSLY CATALYZED C-C COUPLING REACTION

(57) **Abstract:** The invention relates to a process for carrying out a homogeneously catalyzed C-C coupling reaction between an optionally substituted (hetero)aromatic bromide compound and a second reactant, which is chosen from the group of olefins in which at least one of the substituents on the olefinic sp^2 carbon atoms is a hydrogen atom, and the group of organoboron compounds with the formula Ar-B(OR^1)-OR^2, where Ar stands for an optionally substituted (hetero)aryl group and R^1 and R^2 each independently represent H or an alkyl group or, together with the O-atoms to which they are bound and the B-atom, form a ring with 2-5 C-atoms, in the presence of an aprotic dipolar solvent and a base, a palladium salt without a ligand being used as palladium catalyst and the reaction being carried out at a ratio between the quantity of palladium present in the palladium salt and the optionally substituted (hetero)aromatic bromine compound of between 0.00001 and 0.1 mol%, preferably between 0.01 and 0.1 mol%. Preferably the optionally substituted (hetero)aromatic bromide compound contains at least one hetero atom chosen from N, O and S. The second reactant is preferably an optionally substituted, aliphatic olefin with 2-5 carbon atoms, an olefin substituted with a carboxyl group, a carboxyester, a nitrile, an optionally substituted amido group, a nitro group or a halogenated hydrocarbon. In another embodiment the second reactant is preferably an aryl boric acid. As aprotic dipolar solvent dimethylformamide or N-methylpyrrolidinone is preferably chosen.

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PROCESS FOR A HOMOGENEOUSLY CATALYZED C-C COUPLING REACTION

The invention relates to a process for carrying out a homogeneously catalyzed C-C coupling reaction between an optionally substituted (hetero)aromatic bromide compound and a second reactant, which is chosen from the group of olefins in which at least one of the substituents on the olefinic sp^2 carbon atoms is a hydrogen atom, and the group of organoboron compounds with the formula Ar-B(OR^1)-OR^2, where Ar stands for an optionally substituted (hetero)aryl group and R^1 and R^2 each independently represent H or an alkyl group or, together with the O-atoms to which they are bound and the B-atom, form a ring with 2-5 C-atoms, in the presence of a palladium catalyst, an aprotic dipolar solvent and a base.

Homogeneously catalyzed C-C coupling reactions are known from the literature. Examples of such reactions are arylations of olefins and aryl-aryl-couplings, which are described in for example "Metal-catalyzed Cross-coupling reactions", F. Diederich and P.J. Stang Eds., Wiley-VCH, Weinheim, 1998, Chapters 2 and 3. In practice the molar ratio between the quantity of palladium and the optionally substituted (hetero)aromatic bromide compound in these C-C coupling reactions usually lies between 1 and 3 mol% and one or more ligands are present, which are used to prevent the precipitation of metallic palladium. In the framework of the invention ligand is therefore understood to be a compound that is used in order to keep the palladium in solution. Examples of ligands used in practice are given for example in "Metal-catalyzed Cross-coupling reactions", F. Diederich and P.J. Stang Eds., Wiley-VCH, Weinheim, 1998, Chapters 2 and 3. Commonly used ligands are phosphines.

In W.A. Herrmann, V.P.W. Bohm and C.-P. Reisinger, J. Organomet.Chem.,576 (1999), p. 23-41, the recent development of palladacycles is described. Palladacycles are used as palladium catalysts in C-C-coupling reactions at relatively low ratios between the quantity of palladium and the optionally substituted (hetero)aromatic bromide compound, namely between 0.0001 and 2 mol%. Palladacyles are prepared from a palladium salt and ligands, for example o-tolylphosphine, tris(2,4-di-tert-butyl)phosphite or a benzylic thioether, and should thus be regarded as a combination of catalyst and ligand.

A disadvantage of the above processes is that they are expensive. In many cases the ligands used are expensive and may hinder the work up of the reaction mixture after the C-C-coupling reaction. In addition, as a rule large quantities

of catalyst are used relative to the quantity of substrate, which increases the catalyst costs and may hinder the work up of the reaction mixture. For the preparation of palladacycles in particular laborious methods are usually necessary.

The aim of the invention is to provide a cheap, simple and commercially attractive process for homogeneously catalyzed C-C coupling reactions with an optionally substituted (hetero)aromatic bromide compound.

This is accomplished according to the invention by using a palladium salt without a ligand as a palladium catalyst and carrying out the reaction at a ratio of the quantity of palladium present in the palladium salt to the optionally substituted (hetero)aromatic bromide compound between 0.00001 and 0.1 mol%.

In the framework of the invention the quantity of palladium present in the palladium salt is understood to be the quantity of palladium ions present in the total amount of palladium salt added.

Surprisingly, it has been found that with the aid of this simple process, in which no ligand and only very little palladium salt is used, such favourable results are obtained that a cheap process can be developed that in practice is easy to scale up and therefore is pre-eminently suitable for commercial applications. Surprisingly, it has been found that, despite the absence of a ligand, no or hardly any precipitation of the palladium catalyst takes place during the reaction. Surprisingly, the activity of the palladium catalyst appears to be so high that the method according to the invention can be suitably applied in C-C coupling reactions with optionally substituted (hetero)aromatic bromide compounds, which are relatively cheap. This is particularly surprising because such bromide compounds are known to be much less reactive than the corresponding, much more expensive iodine compounds. In the process according to the invention, for instance a conversion of more than 80%, preferably more than 90% in particular more than 95% can be achieved in less than 24 hours, preferably in less than 15 hours, more preferably in less than 5 hours and often even in less than 2 hours.

In the process according to the invention an optionally substituted (hetero)aromatic bromide compound is coupled with an olefin or a organoboron compound.

Suitable examples of (hetero)aromatic groups from which the bromide compound has been derived are phenyl, naphthyl, pyridyl, pyrrolyl, quinolyl, isoquinolyl, furyl, thienyl, benzofuryl, indenyl, pyrimidinile, pyrazolyl and imidazolyl. The (hetero)aromatic group can optionally be substituted with one or more substituents, in

principle all substituents which are inert under the given reaction conditions. Suitable examples of such substituents are an alkyl group with for example 1 to 20 carbon atoms, for example a methyl, ethyl, isobutyl or trifluoromethyl group; an alkenyl group with for example 2 to 20 carbon atoms; a (hetero)aryl group with for example 1 to 50 carbon atoms; a carboxyl group; an alkyl or aryl carboxylate group with for example 2 to 50 carbon atoms; a formyl group; an alkanoyl or aroyl group with for example 2 to 50 carbon atoms; a carbamoyl group; an N-substituted alkyl or aryl carbamoyl group with for example 2 to 50 carbon atoms; an amino group; an N-substituted alkyl or arylamino group with for example 1 to 50 carbon atoms; a formamido group; an alkyl or aryl amido group with for example 2 to 50 carbon atoms; a hydroxy group; an alkoxy or aryloxy group with for example 1 to 50 carbon atoms; cyano; nitro; halogen and an alkyl or arylthio group with for example 1 to 50 carbon atoms. Preferred examples of (hetero)aromatic groups are substituted phenyl groups and fused aromatic groups, for instance groups derived from naphthyl, for example a biphenyl, 4-fluoro-phenyl, naphthyl or 6-chloro-naphthyl group.

In particular the process according to the invention surprisingly also appeared to be applicable to compounds of which the optionally substituted (hetero)aromatic bromide compound contains at least one hetero atom chosen from N, O and S. Suitable examples of such compounds are bromoacetophenones, for example 4-bromoacetophenone; bromopyridines, for example 3-bromopyridine; bromobenzonitriles, for example 2-bromobenzonitrile or 4-bromobenzonitrile; bromobenzaldehydes, for example 2-bromobenzaldehyde or 4-bromobenzaldehyde; bromonitrobenzenes, for example 4-bromonitrobenzene; 2-bromine-6-methoxynaphthalene and bromoanisoles, for example 4-bromoanisole. These compounds have a good activity in the method according to the invention. This is surprising, because the optionally substituted (hetero)aromatic bromide compound is present in a very large excess relative to the palladium catalyst in the method according to the invention and it was expected that this compound would act as a catalyst poison due to the presence of one or more hetero atoms.

In an embodiment of the invention as second reactant an olefin is used with formula (1)

$$R^3R^4C{=}CHR^5 \qquad (1)$$

in which R^3, R^4 and R^5 can each be chosen independently of each other in function of

the desired final product and can represent both electron-donating, electron-withdrawing and electron-neutral groups. Suitable choices for R^3, R^4 and R^5 are: hydrogen; an alkyl group with for example 1 to 20 carbon atoms, for example a methyl, ethyl, or trifluoromethyl group; an alkenyl group with for example 2 to 20 carbon atoms; a (hetero)aryl group with for example 1 to 50 carbon atoms; a carboxyl group; an alkyl or aryl carboxylate group with for example 2 to 50 carbon atoms; a formyl group; an alkanoyl or aroyl group with for example 2 to 50 carbon atoms; a carbamoyl group; an N-substituted alkyl or aryl carbamoyl group with for example 2 to 50 carbon atoms; an amino group; an N-substituted alkyl or arylamino group with for example 1 to 50 carbon atoms; a formamido group; an alkyl or aryl amido group with for example 2 to 50 carbon atoms; an alkoxy or aryloxy group with for example 1 to 50 carbon atoms; cyano; nitro; halogen and an alkyl or arylthio group with for example 1 to 50 carbon atoms.

Preferably one of the three substituents R^3, R^4, R^5, is hydrogen, more preferably two of the three substituents are hydrogen.

Suitable examples of olefins with formula (1) are aliphatic alkenes, for example ethylene, propylene, 1-butene, 2-butene, 1,3-butadiene and 1-decene; acrylic acids, for example acrylic acid, and methacrylic acid; salts of acrylic acids, for example sodium acrylate; acrylate esters, for example methyl acrylate, n-butyl acrylate, t-butyl acrylate, 2-ethyl-hexylacrylate, benzyl acrylate, methyl methacrylate, and n-butyl methacrylate; acrolein; acrolein-dimethyl acetal; olefinic nitriles, for example acrylonitrile and methacrylonitrile; olefinic amides, for example acrylamide and N,N-dimethylacrylamide; maleates, for example di-n-butyl maleate; aromatic alkenes, for example styrene, 2-vinyl naphthalene, 4-vinyl anisole, 4-vinyl aniline, 4-vinyl benzaldehyde, 4-vinyl benzoic acid and 4-vinyl pyridine; olefinic ethers, for example cyclohexyl vinyl ether; 3-butenoic acid; 1-vinyl acetamide; 1-vinyl formamide; vinyl acetate; 1-vinyl-2-pyrrolidone; 1-vinyl-2-caprolactam; vinyl trimethylsilane and sodium salt of vinyl sulphonic acid. Optionally substituted cyclic olefins, for example cyclohexene, indene and cyclooctene, where R^3 and R^4, R^3 and R^5 or R^4 and R^5 from formula (1) together with the carbon atoms to which they are bound form a ring structure, also are olefins that can be suitably used in the method according to the invention. Preferably use is made of optionally substituted aliphatic olefins with 2-5 carbon atoms or olefins substituted with a carboxyl group, a carboxyester, a nitrile, an optionally substituted amido group, a nitro group or a halogenated hydrocarbon.

In another embodiment of the invention use is made of an

organoboron compound with the formula Ar-B(OR^1) -OR^2 as second reactant, where Ar stands for an optionally substituted (hetero)aryl group and R^1 and R^2 each independently represent H or an alkyl group or, together with the O-atoms to which they are bound and the B-atom, form a ring with 2-5 C-atoms. Preferably an optionally substituted (hetero)aryl boric acid or, of course, its anhydride is used. Suitable examples of (hetero)aryl groups and substituents are the same as given above for the (hetero)aromatic bromide compound. Examples of suitable (hetero)aryl boric acids are phenylboric acid and p-tolyl boric acid.

The C-C coupling reaction in the process according to the invention is carried out in the presence of a palladium salt without a ligand. Any arbitrary palladium salt can be used as a catalyst, for example a palladium carboxylate, for example the cheap $Pd(OC(O)CH_3)_2$ or $Pd(OC(O)C_6H_5)_2$, a palladium halide, for example $PdCl_2$, $PdBr_2$ or PdI_2, or a sodium palladium halide, for example Na_2PdCl_4 or Na_2PdCl_6.

The ratio between palladium, calculated as the quantity of palladium in the palladium salt, and the optionally substituted (hetero)aromatic bromide compound lies between 0.00001 and 0.1 mol%, preferably between 0.01 and 0.1 mol% palladium, most preferably between 0.01 and 0.05 mol%.

Suitable solvents that can be used in the process according to the invention are aprotic dipolar solvents, for example dimethyl formamide (DMF), dimethyl acetamide (DMA), 1-methyl pyrrolidinone (NMP), dimethyl sulphoxide (DMSO), acetonitrile or toluene. In specific cases reactants and/or products can serve as a solvent.

The C-C coupling reaction is carried out in the presence of a base in the method according to the invention. Examples of suitable bases are mentioned in for example "Metal-catalyzed Cross-coupling reactions", F. Diederich and P.J. Stang Eds., Wiley-VCH, Weinheim, 1998, Chapters 2 and 3. The base is preferably chosen from the group of tertiary amines, pyridines and alkali metal acetates, alkali metal hydroxides, alkali metal alkoxides, alkali metal phosphates, alkali metal carbonates, and alkali metal hydrogen carbonates. More preferably, the base is chosen from NaOAc, KOAc, K_2CO_3, Na_2CO_3,$CaCO_3$, K_3PO_4, $NaHCO_3$ or trialkylamines, in which the alkyl groups each preferably contain, independently of each other, 1 to 20, in particular 1 to 10 carbon atoms, for example triethylamine, tri(n-butyl)amine, methyldiisopropylamine or methyldicyclohexylamine.

The process according to the invention can be used in the presence of one or more additives that are customary in such reactions and that are mentioned

in for example "Metal-catalyzed Cross-coupling reactions", F. Diederich and P.J. Stang Eds., Wiley-VCH, Weinheim, 1998, Chapters 2 and 3. Additives that can for example be used are phase-transfer catalysts, for example quaternary ammonium salts, in particular tetrabutylammonium chloride or bromide, triethylbenzylammonium bromide, trioctylbenzylammonium chloride, tetrapropylammonium bromide, or tetraethylammonium chloride, and carbonyl compounds, for example (α) -diketones, in particular 1,2-cyclohexanedione, α- hydroxy ketones, for example 2-hydroxycyclohexanone, aliphatic aldehydes and benzoquinone.

The temperature at which the C-C coupling reaction according to the invention is carried out is not particularly critical. One skilled in the art can simply determine the optimum temperature for his specific reaction system. Preferably the reaction temperature lies between 25 and 250°C, more preferably between 50 and 175°C.

The invention will be elucidated with the following examples.

Examples

Definitions

C_{end} = number of moles of product formed at the end of the reaction.
D_0 = number of moles of optionally substituted (hetero)aromatic bromide compound at the start of the reaction.
D_e = number of moles of optionally substituted (hetero)aromatic bromide compound at the end of the reaction.

Yield = C_{end}/D_0 * 100%
Conversion = $(D_0-D_e)D_0$ * 100 %
Selectivity = (yield/conversion) * 100 %

Example I

C-C coupling reaction of 4-bromoacetophenone and n-butyl acrylate

NaOAc (OAc stands for $OC(O)CH_3$) (2.46 g, 30 mmol) and 4-bromoacetophenone (3.03 g, 15.2 mmol) were weighed out into a 50 ml Schlenk vessel. After addition of 27 ml 1-methylpyrrolidinone (NMP) and a magnetic stirrer the Schlenk vessel was closed with a rubber septum. Under a nitrogen atmosphere a

syringe was then used to add, with stirring: $Pd(OAc)_2$ (0.4 mg; 0.0018 mmol, 0.012 mol% relative to 4-bromoacetophenone) dissolved in 3 ml NMP and dihexyl ether (328 mg, 1,76 mmol) as internal standard for GC analysis. The reaction mixture was heated. At 100°C n-butyl acrylate (3.78 g, 29.5 mmol) was added with the aid of a syringe. The reaction mixture was heated to the reaction temperature (130°C) and the conversion was monitored by subjecting drawn samples to GC analysis. After 120 minutes the conversion was 95% and the selectivity to the trans-product was 96%.

Example II

C-C coupling reaction of 3-bromopyridine and n-butyl acrylate

NaOAc (2.46 g, 30 mmol) was weighed out into a 50 ml Schlenk vessel. After addition of 27 ml NMP and a magnetic stirrer the Schlenk vessel was closed with a rubber septum. Under a nitrogen atmosphere a syringe was then used to add, with stirring: 3-bromopyridine (2.57 g, 16.3 mmol), $Pd(OAc)_2$ (0.4 mg; 0.0018 mmol, 0.011 mol% relative to 3-bromopyridine) dissolved in 3 ml NMP and dihexyl ether (355.4 mg, 1.91 mmol) as internal standard for GC analysis. The reaction mixture was heated and at 100°C n-butyl acrylate (3.53 g, 26.2 mmol) was added with the aid of a syringe. The reaction mixture was heated to the reaction temperature (130°C) and the conversion was monitored by GC analysis of drawn samples. After 21.5 hours the conversion was 94% and the selectivity 95%.

After cooling the reaction mixture was poured out into 150 ml water and extracted with 80 ml toluene. The aqueous layer was extracted once again with 50 ml toluene. The collected organic layer was washed with water (3 times 125 ml), saturated aqueous NaCl solution (1 time 150 ml), dried with the aid of Na_2SO_4, and filtered through Celite. The Celite phase material was washed with toluene (1 time 150 ml) and the filtrate was thickened with the aid of a film-type evaporator. ^1H NMR of the light-orange liquid (3.6 g) demonstrated the presence of the coupling product and traces of the starting material and dihexyl ether.

Example III

C-C coupling reaction of 4-bromoacetophenone and n-butyl acrylate on 2.5 litre-scale

Under nitrogen the following materials were introduced into a double-walled 3 litre reactor: $Pd(OAc)_2$ (30.4 mg, 0.135 mmol, 0.0099 mol% relative to 4-bromoacetophenone), 2 litres of NMP, 4-bromoacetophenone (272 g, 1.36 mole), and NaOAc (152 g, 1.85 mole). The reaction mixture was heated to 110°C with stirring and

at that temperature a start was made with the portionwise addition of n-butyl acrylate (300 g, 2.34 mole, in approximately 1 hour). The mixture was meanwhile heated further to 140°C. Within 30 minutes, after all n-butyl acrylate was added, the conversion was > 99% (GC analysis). After cooling to approximately 80°C the reaction mixture was poured out into 1000 g ice and extracted with 800 ml toluene. The aqueous layer was extracted once again with toluene (3 times 400 ml). The collected organic layer was washed with water (3 times 250 ml), saturated aqueous NaCl solution (2 times 150 ml), dried with the aid of Na_2SO_4, and filtered. The filtrate was thickened to 420 g with the aid of a film-type evaporator and analyzed with the aid of GC. The yield of coupled trans-product amounted to 98%.

Example IV

C-C coupling reaction of 3-bromopyridine and n-butyl acrylate on a 2.5 litre scale

Under nitrogen the following materials were introduced into a double-walled 3 litre reactor: $Pd(OAc)_2$ (152 mg, 0.68 mmol, 0.049 mol% relative to 3-bromopyridine), 2 litres of NMP, 3-bromopyridine (220 g, 1.39 mole) and NaOAc (152 g, 1.85 mole). The reaction mixture was heated to 110° with stirring and at that temperature the portionwise addition of n-butyl acrylate was started (300 g, 2.34 mole, in approximately 1 hour). The mixture was meanwhile heated further to 140°C. After 22 reaction hours the conversion was > 99% (GC analysis). After cooling to approximately 80°C the reaction mixture was poured out into 1000 g ice and extracted with 800 ml toluene. The aqueous layer was extracted once again with toluene (3 times 400 ml). The collected organic layer was washed with water (3 times 250 ml), saturated aqueous NaCl solution (2 times 150 ml), dried with the aid of Na_2SO_4, and filtered. The filtrate was thickened to 409 g with the aid of a film-type evaporator and analyzed with the aid of GC. The yield of coupled trans-product amounted to 87%.

Example V

C-C coupling reaction of 3-bromopyridine and t-butyl acrylate

$Pd(OAc)_2$ (3.5 mg; 0.0156 mmol, 0.044 mol% relative to 3-bromopyridine) and NaOAc (3.8 g, 48.3 mmol) were weighed out into a 100 ml Schlenk vessel. 50 ml NMP and a magnetic stirrer were added and the Schlenk vessel was closed with a rubber septum. Under a nitrogen atmosphere and with stirring 3-bromopyridine (5.51 g, 34.9 mmol) was added with the aid of a syringe. The reaction mixture was heated and at 100°C t-butyl acrylate (7.4 g, 57.8 mmol) was added with

the aid of a syringe. The reaction mixture was heated to the reaction temperature (130°C) and the conversion was monitored by GC analysis of drawn samples. After 18 hours the conversion was > 95%.

Example VI

C-C-coupling reaction of bromobenzene and sodium acrylate

In a 50 ml Schlenk tube was added: $Pd(OAc)_2$ (1.6 mg, 0.0071 mmol, 0.041 mol% relative to bromobenzene), bromobenzene (2.7 g, 17.2 mmol), sodium acrylate (2.4 g, 25.6 mmol) and 25 ml of NMP. A magnetic stirrer was added and the Schlenk tube was closed with a rubber stopper. Nitrogen gas was applied and the tube was placed in an oil bath of 135°C and stirred overnight. GC analysis showed a conversion of 86% after 2 hours (98% after 21 hours, no sampling in between) with a selectivity of 98% to the trans-product.

Example VII

C-C-coupling reaction of 4-bromoacetophenone and styrene

In a 25 ml vial was added: $Pd(OAc)_2$ (1.12 mg, 0.0050 mmol, 0.050 mol% relative to 4-bromoacetophenone), 4-bromoacetophenone (1.99 g, 10 mmol), styrene (1.3 g, 12.5 mmol), NaOAc (1.0 g, 12 mmol) and NMP (13 ml). A magnetic stirrer was added and the vial was closed with a plastic cap. The vial was placed in an oil bath of 135°C and stirred magnetically. A sample after 1 hour showed complete conversion. The ratio of trans, cis and methylene product was 94 : 1 : 5, respectively.

Examples VIII to XXX

C-C-coupling reaction of several different aryl bromides and several different olefins

In an automated synthesis robot (ASW 2000, from Chemspeed™) 23 double walled reaction vessels were each filled with NaOAc (~2.7 mmol, slight excess relative to the aryl bromide). The vessels were closed and nitrogen gas was applied. To each vessel was added subsequently NMP (1.5 ml), dihexyl ether (0.50 mmol, internal standard for GC), 2.0 ml of a solution of the aryl bromide (1M in NMP), and 0.25 ml of a solution of $Pd(OAc)_2$ (0.0035 M in NMP, 0.00089 mmol $Pd(OAc)_2$ in each vessel = 0.045 mol% compared to the aryl bromide), by using the fully automated syringe of the robot. All vessels were shaken and heated up to 125°C. The different olefins (2.4 mmol) were added (t = 0) and the vessels were further heated to 135°C. After 1, 2, 5, and 15 hours a sample (0.1 ml) of every vessel was taken. The samples were diluted

and analysed by GC. The results are shown in Table 1.

Table 1

Arylbromide	Olefin	Time (hr)	Conversion (%, by GC)	Product	Yield (%, by GC)
4-bromoacetophenone	*n*-Butylacrylate	1	100	3-(4-Acetyl-phenyl)-acrylic acid butyl ester	99
4-bromobenzaldehyde	*n*-Butylacrylate	1	100	3-(4-Formyl-phenyl)-acrylic acid butyl ester	100
2-bromobenzonitrile	*n*-Butylacrylate	1	100	3-(2-Cyano-phenyl)-acrylic acid butyl ester	95
4-bromobenzonitrile	*n*-Butylacrylate	1	100	3-(4-Cyano-phenyl)-acrylic acid butyl ester	98
4-bromonitrobenzene	*n*-Butylacrylate	1	100	3-(4-Nitro-phenyl)-acrylic acid butyl ester	95
2-bromo-6-methoxynaphthalene	*n*-Butylacrylate	1	100	3-(6-Methoxy-naphthalen-2-yl)-acrylic acid butyl ester	96
4-bromobiphenyl	*n*-Butylacrylate	2	95	3-Biphenyl-4-yl-acrylic acid butyl ester	90
1-bromonaphthalene	*n*-Butylacrylate	2	100	3-Naphthalen-2-yl-acrylic acid butyl ester	91
9-bromophenanthrene	*n*-Butylacrylate	2	100	3-Phenanthren-9-yl-acrylic acid butyl ester	93
4-bromoanisole	*n*-Butylacrylate	5	93	3-(4-Methoxy-phenyl)-acrylic acid butyl ester	94
bromobenzene	*n*-Butylacrylate	15	95	3-Phenyl-acrylic acid butyl ester	90
3-bromopyridine	*n*-Butylacrylate	15	100	3-Pyridin-3-yl-acrylic acid butyl ester	97
4-Bromoanisol	*t*-Butylacrylate	5	91	3-(4-Methoxy-phenyl)-acrylic acid *tert*-butyl ester	90
Bromobenzene	*t*-Butylacrylate	1	96	3-Phenyl-acrylic acid *tert*-butyl ester	94
1-Bromo-2-fluorobenzene	*t*-Butylacrylate	1	100	3-(2-Fluoro-phenyl)-acrylic acid *tert*-butyl ester	100
1-Bromo-3-fluorobenzene	*t*-Butylacrylate	1	100	3-(3-Fluoro-phenyl)-acrylic acid *tert*-butyl ester	100

1-Bromo-4-fluorobenzene	*t*-Butylacrylate	1	100	3-(4-Fluoro-phenyl)-acrylic acid *tert*-butyl ester	100
(4-Bromo-phenyl)-dimethyl-amine	*t*-Butylacrylate	5	88	3-(4-Dimethylamino-phenyl)-acrylic acid *tert*-butyl ester	88
1-Chloro-4-bromobenzene	Styrene	15	99	*Trans*-4-chlorostilbene	92
2-Bromo-6-methoxynaphthalene	Styrene	15	97	2-Methoxy-6-styryl-naphthalene	94
4-Bromoacetophenone	But-3-en-2-ol	15	99	4-(4-Acetyl-phenyl)-butan-2-one	92
1-Chloro-4-bromobenzene	But-3-en-2-ol	15	93	4-(4-Chloro-phenyl)-butan-2-one	88
2-Bromo-6-methoxynaphthalene	But-3-en-2-ol	15	92	4-(6-Methoxy-naphthalen-2-yl)-butan-2-one	86

CLAIMS

1. Process for carrying out a homogeneously catalyzed C-C coupling reaction between an optionally substituted (hetero)aromatic bromine compound and a second reactant, which is chosen from the group of olefins in which at least one of the substituents on the olefinic sp^2 carbon atoms is a hydrogen atom, and the group of organoboron compounds with the formula Ar-B(OR^1) -OR^2, where Ar stands for an optionally substituted (hetero)aryl group and R^1 and R^2 each independently represent H or an alkyl group or, together with the O-atoms to which they are bound and the B-atom, form a ring with 2-5 C-atoms, in the presence of a palladium catalyst, an aprotic dipolar solvent and a base, characterized in that as palladium catalyst a palladium salt without a ligand is used and in that the reaction carried out at a ratio between the quantity of palladium present in the palladium salt and the optionally substituted (hetero)aromatic bromide compound of between 0.00001 and 0.1 mol%.
2. Process according to claim 1, characterized in that the optionally substituted (hetero)aromatic bromide compound contains at least one hetero atom chosen from N, O and S.
3. Process according to claim 1 or 2, characterized in that the second reactant is an optionally substituted, aliphatic olefin with 2-5 carbon atoms.
4. Process according to claim 3, characterized in that the second reactant is an olefin substituted with a carboxyl group, a carboxyester, a nitrile group, an optionally substituted amido group, a nitro group or a halogenated hydrocarbon group.
5. Process according to claim 1 or 2, characterized in that the second reactant is an (hetero)aryl boric acid or its anhydride.
6. Process according to any one of claims 1-5, characterized in that the ratio between the quantity of palladium present in the palladium salt and the optionally substituted (hetero)aromatic bromine compound lies between 0.01 and 0.1 mol%, preferably between 0.01 and 0.05 mol%.
7. Process according to any one of claims 1-6, characterized in that the aprotic dipolar solvent is chosen from dimethylformamide and N-methylpyrrolidinone.
8. Process according to any one of claims 1-7, characterized in that a phase-transfer catalyst is also used.

9. Process according to any one of claims 1-8, characterized in that a carbonyl compound is also used.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/NL 02/00037

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07B37/04 C07C67/343 C07C69/738 C07D213/55 C07C253/30
C07C49/258 C07C255/56 C07C205/45 C07C49/255 C07C49/223
C07C49/217 C07C49/235 C07C225/22 C07C25/24 C07C43/215

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WALLOW T I ET AL: "HIGHLY EFFICIENT AND ACCELERATED SUZUKI ARYL COUPLINGS MEDIATED BY PHOSPHINE-FREE PALLADIUM SOURCES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 59, no. 17, 1994, pages 5034-5037, XP002030761 ISSN: 0022-3263 page 5034, right-hand column, line 3 - line 7 claims 1-13 Tabel 1, ingang 11-15 ---	1-9
X	DE 197 12 388 A (STUDIENGESELLSCHAFT KOHLE MBH) 1 October 1998 (1998-10-01) abstract examples 35,39,44,45 ---	1-9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2002	01/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Diederen, J

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REETZ M T ET AL: "A New Catalyst System for the Heck Reaction of Unreactive Aryl Halides" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 37, no. 4, 1998, pages 481-483, XP002160618 ISSN: 0570-0833 table 1 page 482, right-hand column, paragraph 2 -page 483, left-hand column, paragraph 3 ---	1-9
X	REETZ, M.T., WESTERMANN, E.: "Phosphane free palladium catalyzed coupling reactions: the decisive role of Pd nanoparticles" ANGEW. CHEM. INT. ED., vol. 39, no. 1, 3 January 2000 (2000-01-03), pages 165-8, XP002179534 page 165, right-hand column, paragraph 2 - paragraph 3 page 167, left-hand column, paragraph 3 -right-hand column, paragraph 3 "We assume - colloid." page 166, line 9 - line 13 ---	1-9
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MEHNERT ET AL.: "Palladium-grafted mesoporous MCM-41 material as heterogeneous catalyst for Heck reactions" CHEM. COMMUN., 1997, pages 2215-6, XP002179535 the whole document	1-9
X	BELLER M ET AL: "First palladium-catalyzed Heck reactions with efficient colloidal catalyst systems" JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 520, no. 1, 9 August 1996 (1996-08-09), pages 257-259, XP004036483 ISSN: 0022-328X table 1 page 259, left-hand column, line 9 - line 23	1-9
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 02/00037

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		JP 2001518108 T	09-10-2001
		US 6316675 B1	13-11-2001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MEHNERT ET AL.: "Palladium-grafted mesoporous MCM-41 material as heterogeneous catalyst for Heck reactions" CHEM. COMMUN., 1997, pages 2215-6, XP002179535 the whole document	1-9
X	BELLER M ET AL: "First palladium-catalyzed Heck reactions with efficient colloidal catalyst systems" JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 520, no. 1, 9 August 1996 (1996-08-09), pages 257-259, XP004036483 ISSN: 0022-328X table 1 page 259, left-hand column, line 9 - line 23	1-9
A	JEFFERY: "Highly stereospecific palladium-catalyzed vinylation of vinylic halides under solid-liquid phase transfer conditions" TETRAHEDRON LETTERS, vol. 26, no. 22, 1985, pages 2667-70, XP002179536 the whole document	1
A	BUMAGIN ET AL.: "Palladium-catalyzed phenylation and vinylaton" BULL. ACAD. SCI. USSR DIV. CHEM. SCI. (ENGL. TRANSL.), vol. 39, no. 11, 1990, page 2426 XP002179537 the whole document	1